IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Kenji HASHIMOTO et al. :

Serial No. 10/519,792 : Group Art Unit 1797

Filed on March 28, 2005 : Examiner: Timothy G, Kingan

For: METHOD OF EXAMINING AND DIAGNOSING SCHIZOPHRENIA

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of
Patents and Trademarks,
Washington, D.C. 20231

Sirs:

I, Kenji HASHIMOTO, a citizen of Japan residing at 10-8-3, Inagedai-cho, Inage-ku, Chiba-shi, Chiba 263-0032 Japan, sincerely declare;

That I was born in March 3, 1959 in Fukuoka, Japan;

That I graduated from Faculty of Pharmaceutical Sciences at Kyushu University, Fukuoka, Japan;

That I was an assistant professor at Graduate School of Medicine, Chiba University, Japan, from 2001 to 2003;

That I was an associate professor at Graduate School of Medicine, Chiba University, Japan, from 2003 to 2005;

That I am a Professor and a Vice Chairman of the Center for Forensic Mental Health, Chiba University, Japan, since 2005;

That I am a councilor of the Scientific Societies including

1. Japan Brain Science Society,
2. Japanese Society of Biological Psychiatry,
3. Japanese Society of Neuropsychopharmacology, and
4. Society for Neuroscience;

That I am a member of the editorial advisory board of scientific journals including

1. CNS Agents-Medicinal Chemistry,
2. Recent Patents on CNS Drug Discovery,
3. The Open of Biochemistry Journal,
4. The Open of Medicinal Chemistry Journal, and
5. The Open of Addiction Journal;

That I am a member of the editorial board of scientific

journals including
1. Clinical Psychopharmacology and Neuroscience, and
2. Journal of Receptor, Ligand and Channel Research;

That I am a member of the editorial board and an academic editor of PLoS ONE;

That I am the editor-in-chief of The Open of Clinical Chemistry Journal;

That I published with other research workers, reports on scientific studies including, among others,

1. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the N-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry. 60(6): 572-576, 2003,
2. Glutamate hypothesis of schizophrenia and approach for possible therapeutic drugs. Curr Med Chem-CNS Agents. 4(2): 147-154, 2004,
3. Identification of multiple serine racemase (SRR) mRNA isoforms and genetic analyses of SRR and DAO in schizophrenia and D-serine levels. Biol Psychiatry. 57(12): 1493-1503, 2005,
4. Dysfunction of glia-neuron communication in pathophysiology of schizophrenia. Curr Psychiatry Rev. 1(2): 151-163, 2005,
5. α7 Nicotinic receptor agonists as potential therapeutic drugs for schizophrenia. Curr Med Chem-CNS Agents. 5: 171-184, 2005,
6. Tropisetron improves deficits in auditory P50 suppression in schizophrenia. Schizophrenia Res. 76(1):67-72, 2005, and
7. The NMDA receptor hypofunction hypothesis for schizophrenia and glycine modulatory sites on the NMDA receptors as potential therapeutic drugs. Clin Psychopharmacol Neurosci. 4(1): 3-10, 2006;

That I am an inventor of the above-identified U.S. patent application SN 10/519,792; and

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

STATEMENTS

(1) Tsai discloses measured values of D-serine concentration of the serum of patients with schizophrenia; however, it does not disclose that of healthy person. It should be noted that, at the time of filing of the present application, there existed no motivation for ordinary skilled in the art to measure the D-serine concentration of the serum of healthy person.

(2) At the time of filing of the present application, it was only after the actual measurement of D-serine concentration of the serum of patients with schizophrenia that the artisan could know whether it is higher or lower than that of healthy person. Moreover, ordinary skilled in the art could not predict whether a comparison of the ratio of the D-serine concentration to the total serine concentration between patients with schizophrenia and healthy person reveals a greater difference than a comparison of the raw value of D-serine concentration between patients with schizophrenia and healthy person.

(3) Examiner states that the formation of a ratio of D-serine/Total serine is within the technical reach of ordinary skill in the art of data analysis, because the value of D-serine in samples will vary with the L-serine available for conversion by the serine racemase, the quantity and distribution of the serine racemase in the sample from which the D-serine is extracted, as well as the amount of the sample that is available and subjected to assay (page 3 of the Final Office Action). However, it is not predictable for ordinary skill in the art whether division of the value of D-serine, which varies greatly depending on the external factors, by a specific value of total serine reduces or increases the error.

(4) Snyder (Neurochemical Research, vol.25(5), 2000, pp.553-560) cited by the Examiner teaches that serine racemase has a function not only to convert L-serine to D-serine but also to convert D-serine to L-serine(see the description from the 10th line from the bottom in the right column on page 556). Therefore, D-serine is in equilibrium with L-serine, which

means, for example, when the level of D-serine decreases, the level of L-serine also decreases. However, I and the co-inventors have found a surprising fact that a D-serine concentration in patients with schizophrenia is lower than in healthy individuals, and conversely, an L-serine concentration in patients with schizophrenia is higher than in healthy persons. Thus, the [D-serine concentration] in patients with schizophrenia is significantly lower than in healthy persons, and furthermore, a [ratio of the D-serine concentration to the total serine concentration] in patients with schizophrenia is far significantly lower than in healthy persons. As is shown in Table 1 of the present specification, p-value for difference of D-serine concentration between healthy subject group and schizophrenia group is 0.001, whereas p-value for difference of a ratio of D-serine/total serine is below 0.0001. When the ratio of D-serine/total serine is employed, the p-value becomes 1/10 or below. This means that the diagnosis of schizophrenia using the [ratio of the D-serine concentration to the total serine concentration] is far more accurate than the diagnosis base on the [D-serine concentration]. Such striking effect cannot be conceived with ease by those skilled in the art from the aforementioned prior art.

(5) To conclude, I strongly believe that the present claim 1 and any claim dependent thereon are not obvious from Tsai et al. (Biological Psychiatry 44: 1081-1089, 1998).

Signed at Chiba, Japan on this date: January 28, 2009

Kenji Hashimoto

Kenji HASHIMOTO

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975